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Long-term outcomes of upper tract urothelial carcinoma: A retrospective evaluation of single-center experience in 275 patients

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ABSTRACT

Objective: We aimed to report our 25-year experience on upper tract urothelial carcinoma (UTUC) on a larger number of patients with long-term follow-up at a single tertiary urology institute.

Material and methods: A retrospective study was conducted on 275 patients from 1990 to 2015. Basic patient demographic data with the laboratory and radiologic investigations were collected. We used 1997 TNM classification and the three-tiered WHO grading system. Data were collected using an SPSS® version 21 spreadsheet.

Results: The mean age was 59±11 years, and 88% of all the patients were male. Previous and concurrent bladder tumors were found in 16% and 26%, respectively. Computed tomography gave an overall accuracy of 96%. Open nephroureterectomy and bladder cuff excision was performed for 85%, and the remaining by laparoscopy and nephron-sparing surgeries. Tumor was pelvicalyceal, ureteric, and both in 40%, 40%, and 20% respectively. In 97% of the patients, the tumor was transitional cell carcinoma. Nearly two-thirds of the patients were of low grade and non-invasive in stage. Nearly half of the patients (46%) had bladder tumor recurrence after NU. Bladder, urethral, and contralateral recurrence, distant, local metastasis occurred in 46%, 2%, 1%, 7.5%, and 6%, respectively.

Conclusion: UTUC is a unique disease with synchronous and metachronous urothelial tumor recurrence that requires long-term surveillance. The majority (two-thirds) of the patients are non-invasive in stage of grade II. Tumor stage is of paramount prognostic significance for survival; the five-year survival rate of T1 and T4 is 80% and 0%, respectively.

Keywords: Carcinoma; nephroureterectomy; outcome assessment; upper urinary tract; urothelium.

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Introduction

Upper tract urothelial carcinoma (UTUC) comprises 10% of all renal tumors and 5% of all urothelial malignancies. Because it is a rare disease, it is difficult to conduct prospective studies, and hence the retrospective reviews are the main source for evidence-based clinical guidelines.[1]

The incidence of UTUC has risen over the past 30 years. With a better understanding of the disease, and recent advances in diagnostic and treatment modalities, the number of the published articles on UTUC has doubled in this decade in contrast to the previous one.[2]

Most of the published series on the overall experience in UTUC included small number of patient, and they were outdated.[3-5] Moreover, a few have been published as single-center experience.

Urologists at a tertiary urology institute were interested to report their 25-year experience with a large number of patients. This study serves as a brief guide that will help urologists as well as oncologists in clinical decision-making on such rare disease.

Material and methods

After institutional review board approval (UNC, 81C/2014), we reviewed the hospital's

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electronic database for patients who were diagnosed or managed with UTUC from 1990 to 2015.

Preoperative work-up
The preoperative evaluation included a complete medical history, physical examination, and the standard routine laboratory investigations. Radiologic imaging included ultrasonography (US) that was performed as an initial scanning tool, and intravenous urography (IVU) that was performed in select cases. Computed tomography/CTU was the mainstay for the diagnosis, and magnetic resonance imaging (MRI) was performed if there was a contraindication for contrast administration, or when recommended by the CT report.

Operative procedures
In the majority of patients, cystoscopy, retrograde ureteropyelography, and diagnostic ureteroscopy were performed in a separate session, and any concomitant bladder tumors were resected. Upper urinary tract cytology was obtained by retrograde catheterization and flushing with 3-5 ml of saline solution before contrast administration, and when feasible, upper tract tumors were biopsied. Cup biopsy was performed in all patients using 3F cold cup biopsy forceps.

The majority of the patients were managed by the standard radical nephroureterectomy with bladder cuff (NU+BCE) excision, by either one or two abdominal incisions. A total of 25 cases were performed laparoscopically, and 13 patients were managed with renal-sparing surgery. All surgical techniques were included in the analysis.

Tumor characteristics and pathological evaluation: The tumor was staged according to the 1997 TNM classification. The most conventional three-tiered WHO grading system was used by different pathologists for pathological grading. Tumor location was divided into three groups: renal-pelvic, ureteric, or both. Multifocality was defined as the presence of two or more tumor foci in non-contiguous locations within the ipsilateral renal unit.

Follow-up regimen: In the first two years, office cystoscopy was performed every three months, and a contrast-enhanced CT was performed every six months. From the third to fifth year, a cystoscopy was performed every six months, and a CT was performed annually. Thereafter, by clinical examination, urine analysis and cytology were completed annually.

Patients who developed bladder tumors were treated with transurethral resection and intravesical chemoimmunotherapy. In our protocol, BCG was given for six weeks, which was then followed by check cystoscopy. Patients with no recurrence were given the same protocol monthly for nine months. Those who were found to have recurrence were given the six-week protocol again. Radical cystectomy was offered to invasive bladder tumor or any recurrence beyond the scope of endoscopic resection.

Cancer-specific survival was calculated from the date of the surgery to the last date patients turned up for an appointment or died from causes related to UTUC (e.g., local recurrence or distant metastasis).

Statistical analysis
Data were collected using an IBM Statistical Package for the Social Sciences (IBM SPSS Statistics Corp.; Armonk, NY, USA) version 21 spreadsheet. Mean and standard deviation were used for normally distributed data; otherwise, median and range were used. Frequency and percentage were used for nominal and categorical variables. Cancer-specific survival was tested from the time of surgery using Kaplan-Meier methods and log rank test was used for survival. Cox proportional hazards regression was used for multivariate analysis in a forward-selection strategy. In all tests, the p-value was two-sided, and the significance was set at $p<0.05$.

Results

The mean age of the study population was 59 ± 11 years. The median follow-up period was 32 months (range 18-300 months). The study included 242 men (88%), and the tumor was right-sided in 121 cases (44%). Hematuria with or without flank pain was the most common complaint (55%), and patients' demographics are listed in Table 1.

Ultrasonography was performed for the majority of patients, that is, 264 (96%). It revealed hydronephrosis in 126 patients (48%), while it was normal in 47 patients (18%). IVU was performed in 100 patients (36%). The most common findings were filling defects in 37, no dye execration in 30, and normal findings in 13 patients. CT and /or MRI were/was performed for 270 patients (98%) with an overall accuracy of 96%-97%. With the referral to the final histopathological reports, CT/MRI was accurate to detect the exact locations in 85% of the renal pelvis and 50% of calyceal tumors.

Concomitant bladder tumor was discovered in 68 patients (25%). All were non-invasive (Ta, Tis, or T1), except three cases that had radical cystectomy with NU. Retrograde pyelography study was performed for 124 (45%) patients, and positive findings were reported in 94% of them. Cytology was performed for 119 patients, and 91 cases were reported with suspicion of TCC; the remaining cases were non-suspicious. The correlation between the cytology and final histopathology reported an overall accuracy of selective cytology in 75%.

Table 1. Patients and tumor characteristics (n=275)

Characteristics	Value (%)*	
Gender		
Male	242	(88)
Female	33	(12)
Presentation		
Hematuria	151	(55)
Flank pain	24	(9)
Hematuria and flank pain	74	(27)
Incidentally discovered	12	(4)
Others	17	(5)
History of previous bladder tumor	46	(16)
Concomitant bladder tumor	71	(26)
Surgical approach		
Open	237	(85)
Laparoscopy	25	(10)
Nephron-sparing	13	(5)
Site of the tumor		
Kidney (pelvi-calyceal)	112	(41)
Ureter	112	(41)
Kidney and ureter	51	(18)
Final pathology		
TCC	267	(97)
Non-TCC-UTUC	5	(2)
No malignancies	3	(1)
Tumor grade		
No malignancies	3	(1)
Grade I TCC	14	(5)
Grade II TCC	165	(60)
Grade III TCC	93	(34)
Tumor stage		
No malignancies	3	(1)
T1	176	(64)
T2	36	(13)
T3	59	(21)
T4	1	(1)
Lymph Node Pathology		
N (-)	264	(96)
N (+)	11	(4)
The final size in cm, median (range)		
Renal pelvis tumors		
Length	3 (6-20)	
Width	7 (3-15)	
Third dimension	5 (3-12)	
Ureteric tumors		
Length	4 (1-10)	
Width	2 (0.5-5)	
Third dimension	0.5 (0.2-1)	

*Decimals were removed for simplification. TCC: transitional cell carcinoma; UTUC: upper tract urothelial carcinoma

Ureteroscopic biopsy was performed for 124 patients (45%), which yielded a total of 135 biopsies (94 ureteric and 41 pelvicalyceal tumors). A total of 16 total negative biopsies were reported, and only one was a true negative, leaving 15 as false negative biopsies (nine pelvi-calyceal and six ureteric) who were operated on based on the radiologic findings, with an overall diagnostic accuracy of 87%.

A total of 237 (85%) cases were operated by open surgery. Nephroureterctomy with bladder cuff excision was performed by two incisions (abdominal and pelvic) and single ventral abdominal in 179 and 58 patients, respectively. Eight cases were initially diagnosed with renal tumors; they were managed by radical nephrectomy. A second surgery for uretrectomy and bladder cuff excision was performed when the pathology confirmed urothelial cancer. Two of the eight cases were squamous cell carcinoma of the renal pelvis.

Laparoscopy was performed in 25 cases. The surgery was completed by laparoscopy for bladder cuff excision in ten cases, while a pelvic incision was performed in the remaining cases. Thirteen cases were managed by renal-preservation surgery for ureteric tumors-most of them with single renal or with chronic renal impairment. Surgeries included ureteroureterostomy, distal ureterectomy, or Boari flap.

The final histopathology showed transitional cell carcinoma in 267 patients (97%), squamous cell carcinoma of the renal pelvis in three, small cell carcinoma in one, and adenocarcinoma of the ureter in one patient. Three cases were benign, with no evidence of malignancy. The other histopathological characteristics are shown in Table 1.

Nearly half of the patients, that is 126 (46%), had bladder tumor recurrence after nephroureterectomy, after a median follow-up of 32 months (range 18-300). The majority of those patients (56%) had one recurrence, non-muscle invasive in stage (85%) and of GII (65%). Multivariate analysis showed ureteric tumors (p=0.04) as the only significant predictor for the development of bladder tumors even after eliminating 98 patients with previous and/or concomitant bladder tumor. All non-invasive bladder tumors were treated with endoscopic resection and intravesical chemoimmunotherapy, with the exception of 36 patients, who had invasive or multicentric bladder tumors. Twenty-seven (27/36) were fit for radical cystectomy, and others received radiotherapy. Urethral and other types of recurrence are shown in Table 2. The surgical technique affected neither bladder recurrence, distant metastasis nor local recurrences (p=0.4, 0.7, and 0.8, respectively).

The overall five-year and ten-year survival rates were 60% and 30%, respectively, Figure 1. Tumor stage, presence of micropapillary invasion and positive LN were the only predictors

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Table 2. Recurrence after surgical management of upper tract urothelial carcinoma

Recurrence	N of patients	(%)
Intravesical recurrence	162	(46)
Contralateral recurrence	3	(1)
Distant metastasis	20	(7.5)
Local recurrence *	17	(6)
Urethral recurrence	8	(2)

*Local recurrence is defined as local relapse within the tumor bed or regional nodes

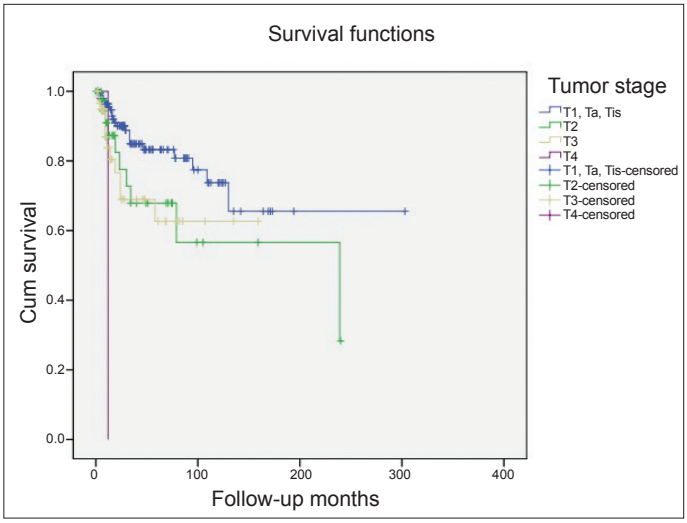

Figure 1. Kaplan-Meier curve of cancer specific survival stratified by tumor T stage

that affected the survival. The results of multivariate analysis using the Cox proportional hazards model showed that tumor stage was the only pathological factor that strongly affected the survival (log rank, p=0.001). The five-year survival for T1, T2, T3, and T4 are 82%, 70%, 62%, and 0%, respectively.

Discussion

In this study, we reported our experience on the long-term outcomes of upper tract urothelial carcinoma at a larger tertiary urology institute on considerable number of patients.

In our study, there were 16% and 26% who had a history of previous non-invasive and concurrent bladder tumor, respectively. Neither affected disease recurrence nor cancer survival, this is in agreement with what has been published.[1,5-7] However, Novara et al.[8] mentioned them as independent predictors of cancer-specific survival probabilities.

Besides cross imaging (CT/MRI), which is the gold standard for the diagnosis of UTUC[9], US had high negative results (18%), and thus it cannot be used for UTUC screening and follow-up. IVU was performed in 100 (36%) patients; it revealed normal findings in 12% of the patients, and had many non-specific findings (hydronephrosis, delayed or no dye excretion). It gave an overall accuracy of 80%, which is similar to that reported by Wang et al.[10].

CT/CTU yielded a high overall accuracy of 96% with similar results reported in many series.[9,11] MRI yielded the same diagnostic accuracy as CT (96%) did, and it was used in patients who had contraindications to contrast administration, or when CT reports were inconclusive. Eight cases were reported as renal parenchymal tumors, which were managed with radical nephrectomy, and the pathology confirmed TCC, a delayed ureterectomy and BCE as performed.

Messer et al.[12] reported low sensitivity of urine cytology in the diagnosis of UTUC, and it had only 76% overall accuracy in our series. With the recent advances in ureteroscopic management for UTUC, the URS biopsy helps in making sound clinical decision. It gave an overall accuracy of 87% in our series. Similar results were also reported by Guarnizo et al.[13]. Due to the high sensitivity and specificity of other non-invasive tests as CTU, we still agree with Potretzke et al.[14] that ureteroscopy can be obviated in select cases.

Nephroureterectomy and bladder cuff excision is the standard management of UTUC, and it was performed in the majority of our patients (85%). Ureteroscopic management of UTUC is an alternative to nephroureterectomy, which is less invasive and preserves renal function. Many series reported its feasibility for small, solitary, low grade/stage tumor, but it requires routine ureteroscopic surveillance and follow-up.[13-16] In our series, few cases that were found with incomplete follow-up data were performed with URS resection. Thirteen cases were operated by segmental ureterectomy, and had a favorable oncological outcome as NU that is similar to the other published series.[17] Most of the tumors were distal ureteric tumors, and distal ureterectomy and Boari flap were the most common surgical procedures.

In our series, transitional cell carcinoma was the pathological type in the vast majority of our patients (97%). There were only three cases of squamous cell carcinoma, one case of small cell carcinoma of the renal pelvis, and one case of adenocarcinoma of the ureter.[7] Similar incidence was reported by Busby et al.[17] (1.9%). But Holmang et al.[18] reported an incidence of 8% of pure SCC. We may contribute the wide range of the incidence of nonTCC in the literature to the subjective pathologic reporting with pure or mixed nonTCC histological types. We have 33 patients (11%) in our series with squamous and glandular differentiation reported with TCC; that is also similar to the incidence in a large multiinstitutional study (14%) that enrolled

more than 1600 patients.[19] Reporting these cases as pure SCC or adenocarcinoma may cause the difference in the incidence of non-TCC.

Bladder recurrence is common (46%), and the incidence in our series was on the upper limit of the range that has reported in the literature.[1] Although many factors may contribute to such recurrence[6], only ureteric tumor location was the risk factor in our series. We have started giving one dose of intravesical chemotherapy (Mitomycin) as an immediate dose post NU. This is based on prospective studies that reported decreased risk by 30%. The absolute reduction in risk is 11%, the relative reduction in risk is 40%, and the number needed to treat to prevent one bladder tumor is 9.[20]

Likewise, Hall et al.[5], who reported one of the largest overall experience series with 252 patients, and in accordance with his series, hematuria was the most common complaint (77%), tumor was left-sided in 50%, prior history of bladder tumor was in 12%, and concomitant bladder tumor was in 20% of the patients. Also, the series had very close pathological criteria, 91% were high grade of GI and GII, and 34% were invasive in stage. However, the series has a relatively larger number of patients who were treated with nephron-sparing surgeries, 17%, in comparison to ours, which had only 4%. Also, they reported a lower bladder recurrence rate than we did (14% versus 46%).

In accordance with 2017 EUA UTUC guidelines[1], the disease is three times more common in males, hematuria is the most common complaint (70%), 17% had concurrent bladder tumor, and the incidence of bladder recurrence is 22%-47%. Also, neither age nor gender is an independent risk factor for cancer survival. However, they reported high incidence of invasive disease (60%), rather than what we and Hall et al.[5] reported (40%). Ureteroscopy was reported to increase the chance of bladder recurrence, but it was not in our series, agreement with Sankin et al.[25] who reported that URS didn't increase the chance of bladder recurrence.

In our series, the overall five-year cancer-specific survival rate was 60% (80%, 70%, 60%, and 0% for T1, T2, T3, and T4, respectively) that is close to that reported in the literature.[1,5] The pathologic tumor criteria are key in patient stratification, and the major determinants of cancer-specific survival. In our series, tumor stage was of paramount prognostic significance for survival of patients with UTUC. Also, tumor grade and LN status were good predictors.[7]

We acknowledge the limitations in our study. We found incomplete data on tobacco use and tumor size. Also, a few cases that were performed with URS resection were found to have incomplete follow-up data. Although our review is a retrospective one, and it is a grade-3 level of evidence, it can be used as a grade-1 recommendation in view of the lack of prospective studies on such a rare disease. It reflects the 25-year experience at a tertiary urology institute with long-term follow-up. This study will help the urologists to facilitate and guide clinical decision-making in managing such rare disease.

In conclusion, UTUC is a unique disease, with synchronous and metachronous tumor recurrence, that requires long-term surveillance. One-third of the patients have multicentric foci, and nearly half of the patients have bladder recurrence. The majority (two-thirds) of the patients have non-invasive tumor in stage of grade II. Tumor stage is of paramount prognostic significance for survival. The five-year survival of T1, T2, T3, and T4 is 80%, 70%, 60%, and 0%, respectively.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of UNC, 81C/2014.

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

Peer-review: Externally peer-reviewed.

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